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# Long-Term Inhaled Corticosteroids in Preschool Children at High Risk for Asthma

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## ABSTRACT

### BACKGROUND

It is unknown whether inhaled corticosteroids can modify the subsequent development of asthma in preschool children at high risk for asthma.

### METHODS

We randomly assigned 285 participants two or three years of age with a positive asthma predictive index to treatment with fluticasone propionate (at a dose of 88 μg twice daily) or masked placebo for two years, followed by a one-year period without study medication. The primary outcome was the proportion of episode-free days during the observation year.

### RESULTS

During the observation year, no significant differences were seen between the two groups in the proportion of episode-free days, the number of exacerbations, or lung function. During the treatment period, as compared with placebo use, use of the inhaled corticosteroid was associated with a greater proportion of episode-free days ($P=0.006$) and a lower rate of exacerbations ($P<0.001$) and of supplementary use of controller medication ($P<0.001$). In the inhaled-corticosteroid group, as compared with the placebo group, the mean increase in height was 1.1 cm less at 24 months ($P<0.001$), but by the end of the trial, the height increase was 0.7 cm less ($P=0.008$). During treatment, the inhaled corticosteroid reduced symptoms and exacerbations but slowed growth, albeit temporarily and not progressively.

### CONCLUSIONS

In preschool children at high risk for asthma, two years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. These findings do not provide support for a subsequent disease-modifying effect of inhaled corticosteroids after the treatment is discontinued. (ClinicalTrials.gov number, NCT00272441.)

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Studies of the natural history of asthma have shown that the initial symptoms commonly occur during the first years of life.[1,2] Children with frequent wheezing (at least four episodes in the prior year) and either one major risk factor (a parental history of asthma or a personal history of atopic dermatitis) or two of three minor risk factors (allergic rhinitis, eosinophilia, and wheezing without colds) are thought to be at high risk.[3] Although daily therapy with inhaled corticosteroids appears to be effective in reducing symptoms in high-risk young children with frequent wheezing,[4-9] the long-term preventive effect of inhaled corticosteroids on asthma after the discontinuation of this treatment has not been investigated in preschool children.[10]

In school-age children, treatment with inhaled corticosteroids is associated with significant improvements in various measures of asthma control; these improvements disappear within months after the inhaled corticosteroids are discontinued.[11-14] We hypothesized that the previous failure to observe a sustained effect on asthma after the discontinuation of inhaled corticosteroids was attributable to the possibility that the intervention was initiated too late in life.[15] We thus designed the Prevention of Early Asthma in Kids (PEAK) clinical trial to determine whether the subsequent development of asthma in high-risk young children with frequent wheezing could be averted by starting inhaled corticosteroids early in life,[16] before the development of persistent disease and chronic loss of lung function.[15]

## Methods

A detailed description of the design of the PEAK trial, including screening and recruitment procedures and statistical analysis, has been reported in detail elsewhere.[16] A description is also provided in the Methods section of the Supplementary Appendix (available with the full text of this article at www.nejm.org).

### Screening and Schedule of Procedures

The PEAK trial was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial of inhaled fluticasone as compared with placebo in children two or three years of age who were at high risk for asthma (Fig. 1A).[16] Children were randomly assigned to receive either the inhaled corticosteroid or placebo for two years, at which point treatment was stopped. The children were then followed for an additional year, during which the primary outcome indicators were measured. The enrolled children had no clinically significant medical disorders apart from wheezing or allergy and were at high risk for the persistence of asthma-like symptoms during their school years, according to a positive modified asthma predictive index (Table 1 of the Supplementary Appendix).[3,17] Only children who had received not more than four months of treatment with inhaled corticosteroids before enrollment and whose asthma symptoms did not require inhaled corticosteroids during a run-in month were eligible. After their parents provided written informed consent, a total of 285 children were randomly assigned, between January 2001 and January 2002, at five clinical centers (as described in the Supplementary Appendix). The schedule of procedures is shown in Figure 1A. Parents of the children were contacted by telephone to collect data on asthma-like symptoms (coughing and wheezing), asthma-medication use, and use of health care resources for respiratory symptoms during the preceding two weeks.

Institutional review boards at all participating centers approved the protocol and consent forms; the trial was monitored by the Childhood Asthma Research and Education (CARE) Network data and safety monitoring board. The role of the commercial sponsors was limited to providing drug and matching placebo, and they did so after reviewing the drafted protocol. The manuscript was made available to all the commercial sponsors (who are listed in the Treatments section) for comments two weeks before finalization. However, all final decisions regarding the study design and the interpretation of data were made exclusively by the National Heart, Lung, and Blood Institute CARE Network steering committee, the members of which vouch for the accuracy and completeness of the data reported.

### Treatments

The randomized treatment period ended in January 2004, and the observation phase ended in January 2005. Children were randomly assigned to one of two study groups: one that was to receive an inhaled corticosteroid (fluticasone propionate [Flovent] at a dose of two 44-$\mu$g puffs twice daily by metered-dose inhaler) and one that was to receive matching placebo (both provided by Glaxo-

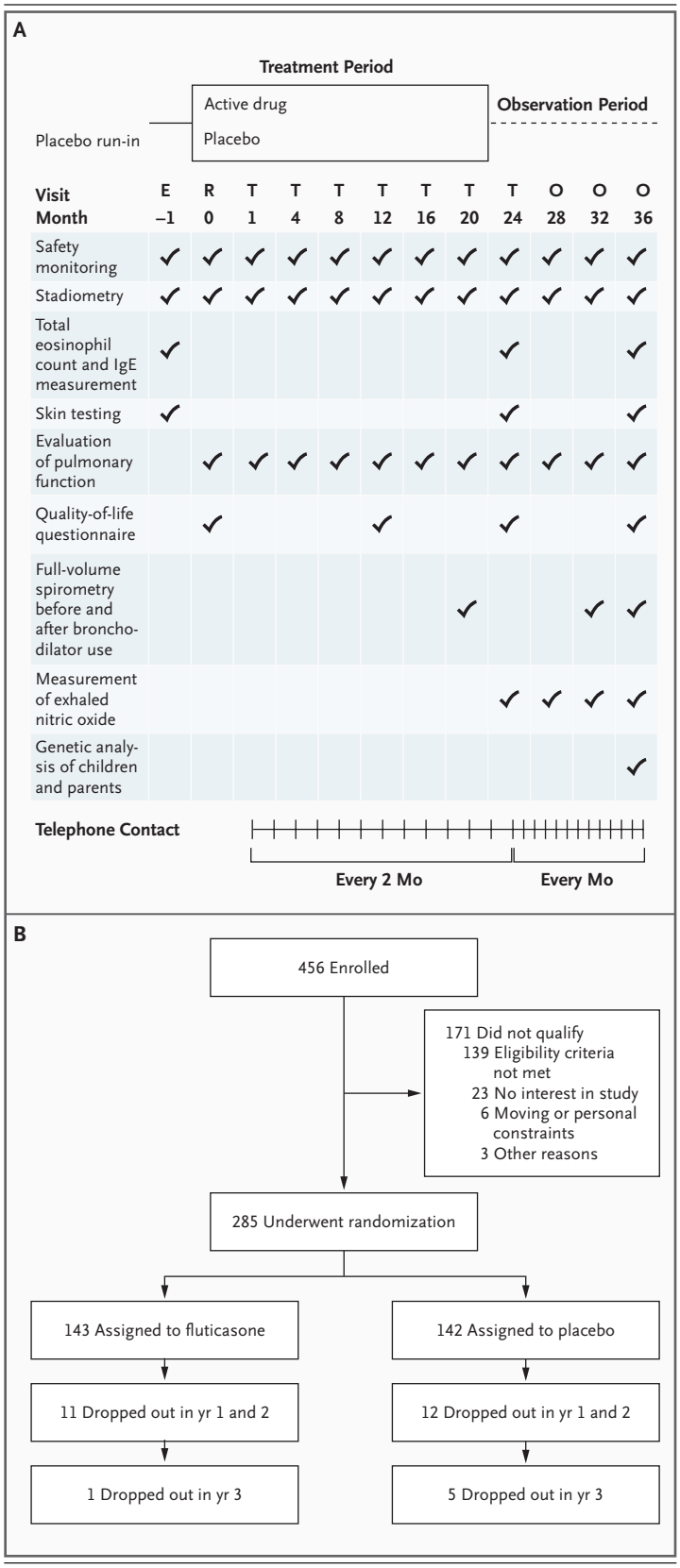


**Figure 1. Schedule of Procedures and Enrollment.**

Panel A shows the schedule of procedures. One group of children received two puffs of fluticasone (44 μg per puff) twice daily and the other group received placebo during the 24-month treatment period. The parents of the children were contacted by telephone every two months during the treatment period and monthly during the observation period. E denotes enrollment into the study, R randomization, T treatment visit, and O observation visit. Modified from Guilbert et al.[16] with the permission of the publisher. Panel B shows the enrollment and treatment assignments. Overall, less than 10 percent of the children were lost to follow-up during the two-year treatment period and less than 12 percent by the end of the observation year.

SmithKline). These inhaled treatments were delivered by means of a valved spacer (AeroChamber) with a mask (provided by Monaghan Medical). Assignments were made with permuted-block randomization, with stratification according to clinic and age group.[16] Adherence was promoted by an educational program[16] and measured with use of an electronic meter (Doser). Rescue therapy in the form of two puffs of albuterol (90 μg per puff) or albuterol nebulization (2.5 mg) (both provided by Schering-Plough) was used according to a written action plan.[16] A four-day course of oral prednisolone (provided by Muro Pharmaceutical) was prescribed according to the protocol for exacerbations, as described previously.[16] The details of the protocols for adding or discontinuing supplementary medications, such as montelukast (Merck), and the criteria for the designation of treatment-failure status are described elsewhere[16] and in the Supplementary Appendix. The PEAK study was extended, and the children continued to be observed through October 2005.

### OUTCOME MEASURES

The primary outcome was the difference between the study groups in the proportion of episode-free days during the year-long observation period. Episode-free days were defined as those during which there were no asthma-like symptoms, no unscheduled medical visits for respiratory symptoms, and no use of any supplementary asthma medications, including albuterol before exercise. Episode-free days were reported by the parents during interviews and were based on two-week recall.[18,19] Secondary outcomes included the proportion of episode-free days during the treatment period.

Other outcomes during both the treatment

period and the observation period included the percentage of eosinophils and the number of courses of systemic corticosteroids and controller medications and the time until their use (Fig. 1A). Impulse oscillometry, which assesses the contribution of resistance and reactance to the total impedance of the respiratory system, was performed according to established procedures (described in the Methods section of the Supplementary Appendix). Reactance at low frequencies reflects the elastic properties of the respiratory system and will have a lower magnitude in patients with airway dysfunction.[20-22] Spirometry was attempted but was successfully completed in only 56 percent of the participants at the end of both the treatment and observation periods, and therefore, the results are not presented in this article. An exacerbation was defined as the need for a course of prednisolone to control asthma-like symptoms, as indicated in the protocol. In addition, potential side effects of long-term use of inhaled corticosteroids on growth were assessed. Height was measured at every visit with an upright stadiometer (Harpenden, Holtain) by established procedures.[16,23] Skin-prick testing, with a core battery of 10 allergens in all the clinical centers and several locally relevant allergens in one center, was performed at enrollment and at the end of the treatment and observation periods[16,17] (as described in the Methods section of the Supplementary Appendix).

### STATISTICAL ANALYSIS

We determined that the enrollment of 280 children would provide the study with a statistical power of 90 percent, at the two-sided 0.05 significance level, to detect a difference between the groups of 10 percentage points in the proportion of episode-free days during the observation year. Primary statistical analyses were carried out according to the intention-to-treat principle. Study data, including data pertaining to growth and nonserious adverse events, were reviewed semiannually by a data and safety monitoring board (as described in the Supplementary Appendix).[16] Serious adverse events were monitored and reviewed continually during the study; there were no formal, a priori stopping rules.

Episode-free days, exacerbations, and use of supplementary asthma medication were assessed by direct contact (by telephone or during a clinic visit) to evaluate asthma symptoms and medication use during the preceding 14 days and the use of health care resources since the last telephone call or clinic visit, as well as by review of the parents' written records of all medication used by the children. Episode-free days were determined from the parents' reported data, which were corrected according to the coordinators' records in cases in which the family did not report previously prescribed supplementary controller medication that had been recorded and dispensed by the coordinators. The proportion of episode-free days for each participant was calculated as the number of episode-free days divided by the number of days of observation. Data from all participants were used in the analysis regardless of the number of days observed.

Episode-free days during the treatment and observation periods were compared by an analysis of covariance (ANCOVA) in which the comparison between treatment groups was made after adjustment for age at randomization, sex, race or ethnic group (non-Hispanic white or other), center, aeroallergen skin-test reactivity (yes or no), duration of asthma-like symptoms at baseline (months), severity of symptoms at baseline (number of episode-free days during the run-in period), percentage of eosinophils, and eczema (yes or no). Episode-free days were converted to the logit scale before analysis in order to satisfy the distributional assumption associated with ANCOVA. For the post hoc analysis of responses, each child was characterized as either having had or not having had an apparent treatment response, separately for the observation year and for the two treatment years combined. These data were analyzed by contingency-table analysis and were summarized with the use of odds ratios. Participants were considered to have had an apparent treatment response if their proportion of episode-free days was greater than 92 percent, which was the median percentage of episode-free days in the group assigned to the inhaled corticosteroid during the two treatment years.

ANCOVA and contingency-table and regression analyses were carried out with use of SAS statistical software (version 8.2). All statistical tests were carried out at the two-sided 0.05 significance level. Additional details of all the analyses are provided in the Methods section of the Supplementary Appendix.

**Table 1. Characteristics of the Children at Baseline, the End of the Treatment Period, and the End of the Observation Period.***

| Characteristic | Baseline | | End of 2-Yr Treatment Period | | End of 1-Yr Observation Period | |
|---|---|---|---|---|---|---|
| | Fluticasone (N=143) | Placebo (N=142) | Fluticasone (N=132) | Placebo (N=130) | Fluticasone (N=131) | Placebo (N=125) |
| Age — yr | 3.0±0.6 | 3.0±0.6 | | | | |
| Race or ethnic group — no. (%)† | | | | | | |
| Non-Hispanic white | 76 (53.1) | 76 (53.5) | | | | |
| Non-Hispanic black | 17 (11.9) | 21 (14.8) | | | | |
| Hispanic | 29 (20.3) | 26 (18.3) | | | | |
| Other | 21 (14.7) | 19 (13.4) | | | | |
| Sex — no. (%) | | | | | | |
| Female | 55 (38.5) | 53 (37.3) | | | | |
| Male | 88 (61.5) | 89 (62.7) | | | | |
| Age at onset of asthma symptoms — yr | 0.97±0.7 | 0.93±0.6 | | | | |
| Age at first asthma diagnosis by a doctor — yr | 1.46±0.9 | 1.28±0.8 | | | | |
| Parental history — no. (%)‡ | | | | | | |
| Asthma | 94 (65.7) | 90 (63.4) | | | | |
| Atopy | 86 (60.1) | 78 (54.9) | | | | |
| Exposure to cigarette smoke during first 2 yr of life — no. (%)‡ | 39 (27.3) | 43 (30.3) | | | | |
| Pets in house — no. (%)‡ | 66 (46.2) | 63 (44.4) | | | | |
| Features recorded during enrollment mo‡ | | | | | | |
| Symptom-free days — %§ | 72.6±24.2 | 74.4±24.3 | | | | |
| Albuterol use — days/wk | 1.0±1.1 | 1.1±1.5 | | | | |
| Night awakenings due to asthma-like symptoms — days/mo‡ | 2.2±2.9 | 2.2±3.8 | | | | |
| ≥1 Visit to emergency department for asthma exacerbation in yr before enrollment — no. (%)‡ | 67 (46.9) | 66 (46.5) | | | | |
| ≥1 Hospitalization for asthma exacerbation in yr before enrollment — no. (%)‡ | 10 (7.0) | 10 (7.0) | | | | |
| Height — cm¶ | 94.9±6.1 | 94.7±5.4 | 107.8±6.4 | 108.7±5.4 | 114.3±6.4 | 115.1±5.4 |
| Positive aeroallergen skin test — no./total no. (%) | 88/143 (61.5) | 81/142 (57.0) | 75/127 (59.1) | 74/117 (63.2) | 72/130 (55.4) | 68/121 (56.2) |
| Eczema — no. (%)‡ | 83 (58.0) | 70 (49.3) | | | | |
| IgE — IU‖ | 42.5±5.4 | 37.7±5.1 | 70.3±5.9 | 62.8±5.6 | 85.0±5.3 | 72.8±5.2 |
| Blood eosinophils — %** | 4.5±3.3 | 3.6±2.7 | 4.0±2.8 | 4.2±3.3 | 4.9±3.8 | 4.3±4.8 |

* Plus–minus values are means ±SD.
† Race was reported on a questionnaire by the children's parents.
‡ This variable was not reevaluated at the end of treatment and observation periods.
§ A symptom-free day during the run-in period, as recorded by the children's parents on diary cards, was defined as a day with no nocturnal awakenings, no use of albuterol for symptoms or use of other asthma medications, no need for unscheduled physician visits, no cold or cold symptoms, and no asthma symptoms.
¶ $P<0.001$ for the comparison between the groups at the end of the treatment period, and $P=0.008$ for the comparison between the groups at the end of the observation period.
‖ Values are geometric means ± geometric SD.
** $P=0.01$ for the comparison between the groups at the baseline visit.

## RESULTS

### STUDY POPULATION

The two study groups were similar with respect to all baseline characteristics (Table 1), except that the group assigned to receive the inhaled corticosteroid had a higher percentage of peripheral-blood eosinophils. There were no significant differences between the groups in the numbers of completed clinic visits or telephone contacts, dropouts, treatment failures, or serious adverse events. Less than 12 percent of the participants in each group were lost to follow-up (i.e., dropped out) (Fig. 1B). Children in whom treatment was deemed to have failed continued to be followed in the CARE clinics. Adherence to treatment, defined as the mean (±SD) percentage of days in which a child took the prescribed dose of study medication, as measured by an electronic meter, was similar in the two study groups (74±0.8 percent in the group assigned to inhaled fluticasone and 69±0.8 percent in the placebo group, P=0.10).

### HEALTH OUTCOMES

*Observation Year*

The proportion of episode-free days during the observation year, after discontinuation of the study drug, was not significantly different between the

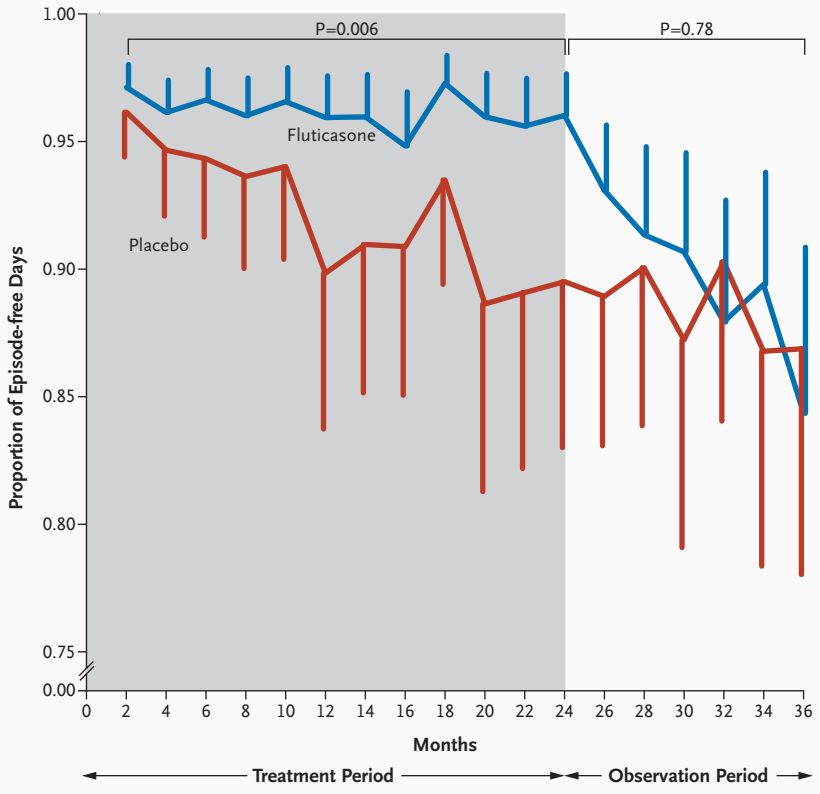


**Figure 2. Bimonthly Proportion of Episode-free Days during the Two-Year Treatment Period and the Observation Period.**

Fluticasone treatment, as compared with placebo, did not increase the proportion of episode-free days during the observation year (86.8 percent [95 percent confidence interval, 81.2 percent to 90.9 percent] vs. 85.9 percent [95 percent confidence interval, 79.9 percent to 90.3 percent], P=0.78), but during the two-year treatment period (shaded area) it significantly increased the proportion of episode-free days (93.2 percent [95 percent confidence interval, 91.1 percent to 94.9 percent] vs. 88.4 percent [95 percent confidence interval, 84.9 percent to 91.2 percent], P=0.006). The proportions of episode-free days in the fluticasone group and the placebo group were 97 percent and 96 percent, respectively, during the first two months of the treatment period; 96 percent and 89 percent during the last two months of the treatment period; and 84 percent and 87 percent during the last two months of the observation year — results that demonstrate an increase in the frequency of asthma-like symptoms over time. The two study groups were compared by analysis of covariance at each two-month interval. P values are for the comparison between the groups at each interval. Vertical bars represent 95 percent confidence intervals.

study groups, at 86.8 percent (95 percent confidence interval, 81.2 to 90.9 percent) in the group assigned to the inhaled corticosteroid and 85.9 percent (95 percent confidence interval, 79.9 to 90.3 percent) in the placebo group (P=0.78) (Fig. 2). In addition, there were no significant differences between the study groups in the rate of use or the time to the initiation of systemic corticosteroid or montelukast treatment or in the rate of hospitalization.

A similar percentage of participants in the two groups used open-label inhaled corticosteroids for two or more months during this period (Table 2). However, children in the group assigned to receive inhaled fluticasone used such open-label treatment for fewer days (20.1 days; 95 percent confidence interval, 16.5 to 24.6) than those in the placebo group (27.0 days; 95 percent confidence interval, 22.5 to 32.7; P=0.007) (Table 2). A possible carryover effect of the use of inhaled corticosteroids during treatment may account for this finding, since the proportion of children in the fluticasone group who required supplementary inhaled corticosteroids was significantly lower than that in the placebo group during the first three months of the observation year (5 percent [95 percent confidence interval, 1 to 8 percent] vs. 10 percent [95 percent confidence interval, 5 to 15 percent], P=0.05), but not thereafter (23 percent [95 percent confidence interval, 15 to 30 percent] vs. 25 percent [95 percent confidence interval, 16 to 33 percent], P=0.82). Unadjusted comparisons between the treatment groups yielded similar results.

*Two-Year Treatment Period*

During the two-year treatment period, the proportion of episode-free days was significantly greater in the fluticasone group than in the placebo group (93.2 percent [95 percent confidence interval, 91.1 to 94.9 percent] vs. 88.4 percent [95 percent confidence interval, 84.9 to 91.2 percent], P=0.006) (Fig. 2). In addition, during the treatment period, the group assigned to inhaled corticoste-

**Table 2. Symptom Control and Impulse-Oscillometric Outcomes during the Treatment and Observation Periods.***

| Variable | End of 2-Year Treatment Period | | | End of 1-Year Observation Period | | |
|---|---|---|---|---|---|---|
| | Fluticasone | Placebo | P Value | Fluticasone | Placebo | P Value |
| Exacerbations requiring a course of systemic corticosteroid — no./100 child-yr (95% CI) | 57.4 (49.0–67.3) | 89.4 (78.3–102.2) | <0.001 | 85.5 (70.9–103.2) | 82.5 (68.0–100.1) | 0.78 |
| Unscheduled physician visits — no./100 child-yr (95% CI) | 79.0 (68.7–90.7) | 83.9 (73.3–96.1) | 0.51 | 108.1 (90.6–129) | 88.0 (72.2–107.1) | 0.11 |
| Hospitalizations — no./100 child-yr (95% CI) | 1.05 (0.34–3.25) | 1.76 (0.73–4.23) | 0.47 | 0.76 (0.11–5.38) | 1.54 (0.39–6.15) | 0.55 |
| Bronchodilator use — mean no. of days/yr (95% CI)† | 14.4 (10.8–18.0) | 18.0 (14.4–21.6) | 0.07 | 18.0 (14.4–21.6) | 18.0 (14.4–21.6) | 0.73 |
| Montelukast use — mean no. of days/yr (95% CI)† | 11.4 (9.3–13.7) | 24.2 (20.5–27.9) | <0.001 | 22.2 (18.3–27.3) | 25.8 (21.3–31.2) | 0.22 |
| Montelukast use for ≥2 mo — no./total no. (%) | 14/143 (9.8) | 30/142 (21.1) | 0.008 | 21/132 (15.9) | 24/130 (18.5) | 0.61 |
| Supplemental use of fluticasone — mean no. of days/yr (95% CI)† | 8.3 (6.8–10.4) | 17.6 (14.9–20.9) | <0.001 | 20.1 (16.5–24.6) | 27.0 (22.5–32.7) | 0.007 |
| At least 2 mo of open-label inhaled-corticosteroid use — no./total no. (%) | 10/143 (7.0) | 19/142 (13.4) | 0.08 | 24/132 (18.2) | 25/130 (19.2) | 0.86 |
| Reactance at 5 Hz at end of period — kPa/liter/sec | –0.39±0.12 | –0.44±0.14 | 0.008 | –0.38±0.12 | –0.38±0.12 | 0.83 |
| Resistance at 5 Hz at end of period — kPa/liter/sec | 1.01±0.20 | 1.05±0.20 | 0.09 | 0.95±0.19 | 0.94±0.19 | 0.61 |

* Plus–minus values are means ±SD. SDs were estimated from the regression model. Means have been adjusted for age at randomization, sex, race or ethnic group (non-Hispanic white vs. all other), center, aeroallergen skin-test reactivity (yes vs. no), duration of symptoms at baseline, severity of symptoms at baseline, percentage eosinophils at baseline, and eczema at baseline (yes vs. no). CI denotes confidence interval.
† Values are based on annualized two-week recall data based on parents' reports. In addition, values reported for the two-year treatment period have been annualized for comparison with values reported for the one-year observation period.

roids had a lower rate of exacerbations necessitating a course of systemic corticosteroids than did the placebo group (57.4 per 100 child-years [95 percent confidence interval, 49.0 to 67.3] vs. 89.4 per 100 child-years [95 percent confidence interval, 78.3 to 102.2], P<0.001), less montelukast use (a mean of 11.4 days per year [95 percent confidence interval, 9.3 to 13.7] vs. a mean of 24.2 days per year [95 percent confidence interval, 20.5 to 27.9], P<0.001), and less supplementary use of fluticasone (i.e., use apart from that assigned in the study) (a mean of 8.3 days per year [95 percent confidence interval, 6.8 to 10.4] vs. a mean of 17.6 days per year [95 percent confidence interval, 14.9 to 20.9], P<0.001), but there was no significant difference between the groups in unscheduled visits to a physician or bronchodilator use (Table 2).

The time to the first course of systemic corticosteroids was also not significantly different between the study groups (P=0.26). However, the times to the second course of systemic corticosteroids (P=0.009 at 12 months) and to the initiation of treatment with montelukast (P=0.005), supplementary fluticasone (P=0.02), or other nonassigned asthma-controller medications (P=0.01) were significantly longer in the group assigned to inhaled corticosteroids than in the placebo group (Fig. 3). No deaths, intubations, or hypoxic seizures during an exacerbation of asthma occurred in either group during the study.

### TREATMENT RESPONSE AND OBSERVATION-YEAR OUTCOMES

In a post hoc analysis, more children in the group assigned to inhaled corticosteroids than in the placebo group were considered to have had an apparent response during the treatment period (proportion of episode-free days, >92 percent) (Table 3). In contrast, the proportion of children with a response who had a worsening (proportion of episode-free days, ≤92 percent) during the observation year was significantly greater in the fluticasone group than in the placebo group. No significant difference between the treatment groups was seen during the observation year among the children who were considered not to have had a response during the treatment period (Table 3).

### MEASURES OF PULMONARY FUNCTION

There was no significant difference between the study groups in any measure derived from impulse oscillometry at the end of the observation period (Table 2). In contrast, at the end of the treatment period, there was a significant reduction in the absolute magnitude of reactance at 5 Hz (−0.39±0.12 vs. −0.44±0.14 kPa per liter per second, P=0.008) and a trend toward a decrease in respiratory resistance at 5 Hz (1.01±0.20 vs. 1.05±0.20 kPa per liter per second, P=0.09) in the inhaled-corticosteroid group as compared with the placebo group (Table 2).

### MEASURES OF GROWTH

At the end of the observation year, the mean increase in height, relative to baseline, in the group assigned to inhaled fluticasone was 0.7 cm less than that in the placebo group (19.2±2.2 cm vs. 19.9±2.2 cm, P=0.008). This difference in the mean increase in height was smaller than the 1.1-cm difference observed at the end of the two-year treatment period (12.6±1.9 cm vs. 13.7±1.9 cm, P<0.001) (Fig. 4). The difference in growth was detected during the first 12 months of inhaled-corticosteroid treatment as a difference in growth velocity between the study groups (6.6±1.0 cm per year in the fluticasone group vs. 7.3±1.0 cm per year in the placebo group between months 1 and 8, P=0.005) and a difference in the mean increase in height (4.5±1.1 vs. 4.9±1.1 cm, between months 4 and 12, P=0.001) (Fig. 4). During the last 12 months of the treatment period, the growth velocity was similar in the study groups, and during the observation year the growth velocity in the inhaled-corticosteroid group was greater than that in the placebo group (7.0±0.8 cm per year vs. 6.4±0.9 cm per year from months 24 to 32, P=0.001) (Fig. 4). Children in the inhaled-corticosteroid group had an average height percentile of 51.5±29.2 as compared with 56.4±27.3 among the children in the placebo group at the end of treatment (P<0.001) and a height percentile of 54.4±27.9 as compared with 56.4±26.9 at the end of observation (P=0.03).

## DISCUSSION

In the PEAK trial, despite treatment of half the patients with an inhaled corticosteroid for two years, there was no effect on asthma-related outcomes during the observation year, after the corticosteroid treatment was stopped. The failure to observe a disease-modifying effect in the observation year cannot be attributed to an insufficient

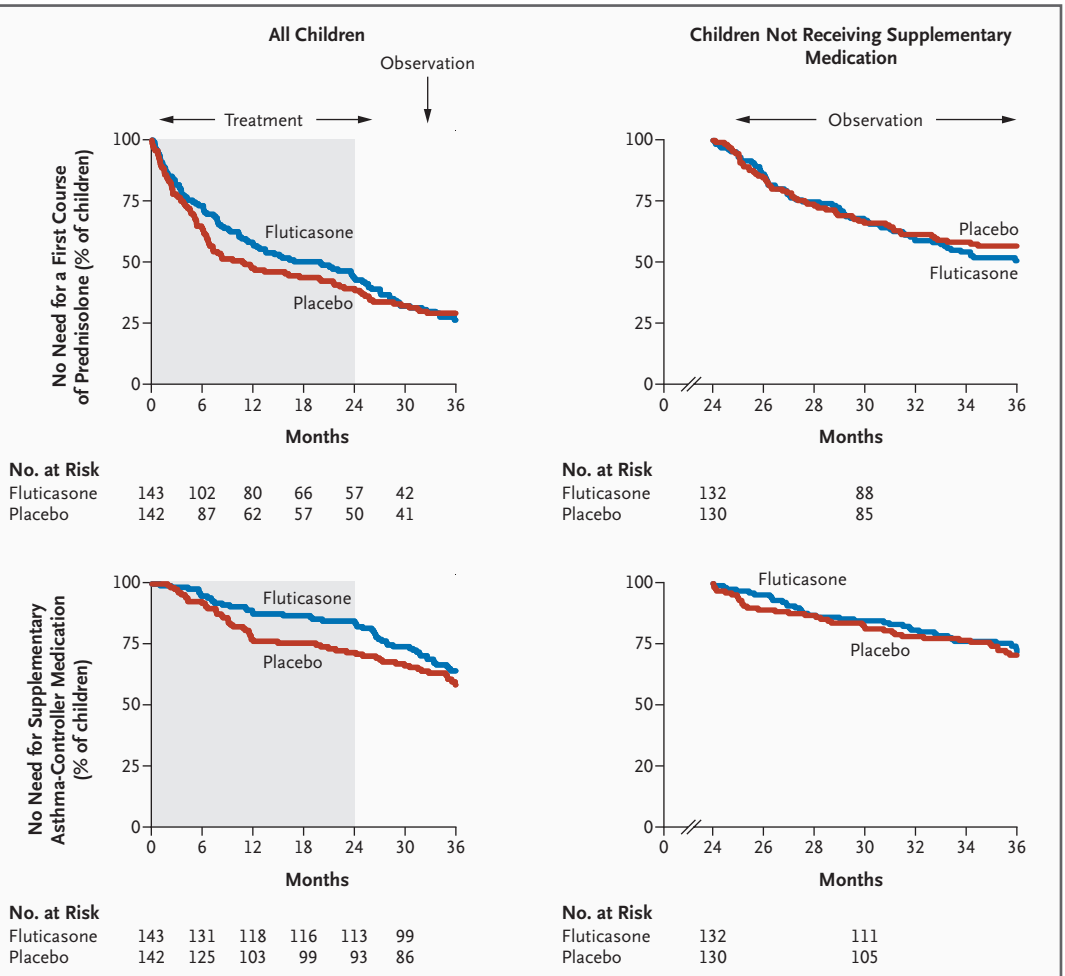


**Figure 3. Kaplan–Meier Estimates of the Time to a First Course of Prednisolone or Initiation of Any Supplementary Asthma-Controller Medication.**

The estimates were calculated for the observation year of the study with data from the children who were not receiving supplementary medication at the beginning of the observation year and for the entire three-year study period with data from all the enrolled children. P values are those associated with comparison (by the log-rank test) of the two study groups during the specified time. There was no significant difference between the groups in the time to a first course of prednisolone (P=0.51 from 24 to 36 months and P=0.61 from 0 to 36 months). The time to the initiation of any supplementary asthma-controller medication (fluticasone, montelukast, or other nonassigned asthma medication) was not significantly longer in the fluticasone group than in the placebo group during the observation period but was longer during the treatment period (P=0.99 from 24 to 36 months, P=0.01 from 0 to 24 months, and P=0.34 from 0 to 36 months).

dose of fluticasone during the treatment period, since this agent affected both the burden of symptoms and somatic growth. Our findings indicate that these children had a considerable burden of symptoms, were at high risk for asthma, and had symptomatic benefit from daily therapy with an inhaled corticosteroid during the two-year treatment period. Like the study by Nielsen and Bisgaard,[21] who analyzed impulse-oscillometric data in a similar population, the current study demonstrated that reactance at 5 Hz was less negative with the use of inhaled corticosteroids than with placebo. A lower absolute magnitude of respiratory-system reactance is a possible indicator of greater dynamic lung compliance,[20-22] and therefore, this finding appears consistent with the other study outcomes, such as those pertaining to symptom burden, exacerbations, and supplementary-medication use.

Clinical improvement was observed while the

**Table 3. Likelihood of Symptoms during the Observation Year, According to the Apparent Response to Inhaled Corticosteroids and Placebo during the Two-Year Treatment Period.**

| Response Group and Symptom Status during Observation* | Fluticasone | Placebo | Odds Ratio for Symptoms (95% CI) |
|---|---|---|---|
| | *no./total no. (%)* | | |
| Children with a response during treatment† | | | |
| Decrease in symptoms during observation | 31/67 (46.3) | 36/54 (66.7) | |
| Increase in symptoms during observation | 36/67 (53.7) | 18/54 (33.3) | 2.32 (1.11–4.88) |
| Children without a response during treatment‡ | | | |
| Decrease in symptoms during observation | 20/65 (30.8) | 21/76 (27.6) | |
| Increase in symptoms during observation | 45/65 (69.2) | 55/76 (72.4) | 0.86 (0.41–1.78) |

* A child was considered to have a response if the proportion of episode-free days during the two-year treatment period was greater than 92 percent (i.e., greater than the median response in the fluticasone group during the treatment period). A child was considered not to have had a response if the proportion of episode-free days during the two-year treatment period was 92 percent or less (i.e., equal to or below the median response in the fluticasone group during the treatment period).

† The odds ratio suggests that the number of symptoms during the observation year among the children who had a response during the treatment period differed according to treatment group. Specifically, children in the fluticasone group who had a response had more asthma-like symptoms during the observation year than did those in the placebo group.

‡ The odds ratio suggests that the number of symptoms during the observation year among the children who did not have a response during the treatment year did not differ significantly between the treatment groups.

children were treated with the inhaled corticosteroid but disappeared after treatment had been discontinued. Our data suggest that inhaled corticosteroids have little therapeutic effect on the processes that determine the progression of the disease from its initial, intermittent stages to a more chronic form, as described in the epidemiology literature.[1,2,24-27]

Elsewhere in this issue of the *Journal* and concordant with our findings, Bisgaard et al.[28] report on the lack of effect of treatment with inhaled corticosteroids on the progression from episodic to persistent wheezing. In their study, no short-term benefit of episodic inhaled corticosteroids was demonstrated. This may be the result of the cohort's younger age, lower frequency of wheezing episodes before enrollment in the study, and the use of intermittent therapy three days after the onset of symptoms, rather than at the onset of symptoms.

On the basis of the burden of disease observed in the children enrolled in the trial, it appears that the use of a modified asthma predictive index was successful in identifying a group of children at high risk for continued asthma-like symptoms. In fact, these children had an increase in the frequency of asthma-like symptoms over time, and approximately 40 percent had an exacerbation that necessitated the use of oral corticosteroids during the observation year. The PEAK cohort was younger and had less frequent symptoms than the 5-to-12-year-old children with mild-to-moderate persistent asthma who were enrolled in the Childhood Asthma Management Program Research study,[12] but the atopic characteristics (personal and family histories of atopy, food and aeroallergen sensitization, and eosinophilia)[16] were similar in the two populations.

One might speculate that if therapy had been initiated before two years of age, the natural course of asthma might have been changed. However, starting long-term treatment without a valid predictive index in children with recurrent wheezing who are not yet two years of age would mean the unnecessary treatment of many children who will eventually outgrow their disease (i.e., those who wheeze transiently)[15,29] and thus would be ethically questionable.

Moreover, one could speculate that the children who had a favorable response to inhaled corticosteroids during the treatment period would constitute the group most likely to have a sustained benefit during the observation year. In fact, post hoc analysis suggests that the opposite was true. Although more children in the inhaled-corticosteroid group than in the placebo group had a response during the treatment period, a greater proportion of them had worsening during the observation year, after the study medication was discontinued — a pattern similar to that in

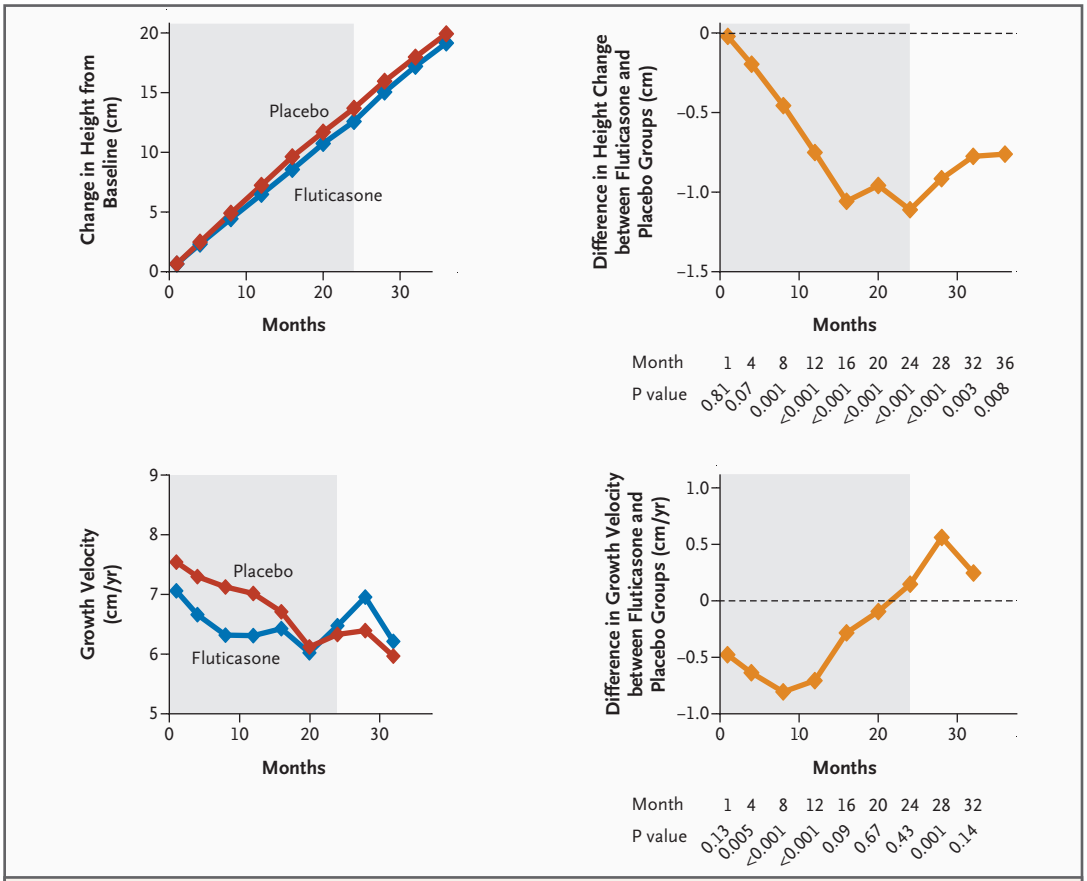


**Figure 4. Height Velocity and Growth during the Three-Year Study.**

The mean differences between the study groups (fluticasone minus placebo) were evaluated by analysis of covariance. The mean increase in height from baseline was 1.1 cm less in the fluticasone group than in the placebo group at the end of the 24-month treatment period and 0.7 cm less at the end of the observation year (top graphs). This significant decrease in growth in the fluticasone group was detectable during the first eight months of treatment as a difference in growth velocity (bottom left graft) and a difference in height (top right graph). At the end of the treatment period, growth velocity was similar in the two study groups, and during the observation period the growth velocity in the fluticasone group was higher than that in the placebo group (bottom graphs). P values are for the comparison between the groups at each visit indicated.

adults and older children with persistent asthma.[11,13,14] These data do not imply that inhaled corticosteroids worsened the children's condition, since the two treatment groups had a similar burden of disease during the observation year.

A reduction in growth velocity was observed in the group assigned to inhaled corticosteroids during the first year of treatment. This observation differs from the normal growth velocities reported in a study of fluticasone treatment for one year[5] among preschool children with recurrent wheezing. In that study, the use of a larger volume spacer for medication delivery,[5,30] which may have led to a different corticosteroid-deposition pattern or to a lower adherence or higher dropout rate,[5] may explain the difference in our findings. Although the observed growth rate in the placebo group was similar to that in the inhaled-corticosteroid group during the last 12 months of treatment, and although growth accelerated during the observation year, there remained a difference of 0.7 cm in height between the treatment groups at the end of the trial. It remains to be determined whether height will become similar in the two groups as the cohort matures, in a manner similar to that observed in older children.[31]

Our data show that the natural course of asthma in young children at high risk for subsequent asthma is not modified by two years of treatment

with inhaled corticosteroids. The treatment, however, did reduce the burden of illness. Our findings demonstrate that inhaled corticosteroids can be used to control active disease but should not be used to prevent asthma in high-risk preschool children.

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